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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/698,323	ISNER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Note that the specification as filed contains claim "1A" (page 44 of the specification). Per 35 CFR 1.126, originally filed claims "1A"-48 have been renumbered as claims 2-49. Therefore, there are 49 originally filed claims in the application.

Applicants' amendments filed on January 09/2002 (Paper No. 8) and on June 06, 2002 (Paper No. 12) have been entered. It is apparent from the Amendment on filed on June 06, 2002 that Applicants have cancelled all originally filed claims, renumbered claims 1-49. Per 35 CFR 1.126, new claims 49-78 in the Amendment on Paper No. 12 have been renumbered 50-79. To avoid any confusion in future Amendments, renumbered claims 50-79 should be used.

Claims 50-79 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Claim Objections

Claim 51 is objected because it contains abbreviations "GM-CSF", "M-CSF", "SCF", "HGF" and others that should have been written in full at the first occurrence of the abbreviations.

Claim 53 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper

dependent form, or rewrite the claim(s) in independent form. This is because the limitation "the increase in frequency of the EPC is at least about 20% as determined by a standard EPC isolation assay" is already present in claim 52 from which claim 53 is dependent upon.

Claim 59 is objected because it contains a misspelled term "vasculanzation" on line 1 of the claim.

Claim 64 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because claim 64 recites "the mammal has, is suspected of having, or will have ischemic tissue", whereas the mammal in claim 50 is already having chronic or acute ischemia, and that claim 64 is dependent on claim 50.

Claim 68 is objected to because of the following informalities: presumably the term "agent" is missing in the claim. Appropriate correction is required.

Claims 68 and 70 are objected because they are identical in scope as claims 69 and 71, respectively. Appropriate correction is required.

Following is a new ground of rejection.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-51 and 55-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The instant claims are drawn to a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia, wherein the method comprises administering to the mammal an effective amount of **a vascularization modulating agent** sufficient to form the new blood vessels in the mammal, and increasing endothelial progenitor cell frequency by at least about 20% as determined by a standard EPC isolation assay. Apart from disclosing vascularization modulating agent such as GM-CSF, VEGF, SLF, SDF-1, G-CSF, HGF, angiopoietin-1, angiopoetin-2, M-CSF, b-FGF and FLT-3 ligand, all of which are **hematopoietic proteins that increase mobilization of hematopoietic progenitor cells and induce angiogenesis**, the instant specification fails to disclose any other substances (e.g., carbohydrates, lipids,

small organic or inorganic molecules), such that these substances are capable of inducing the formation of new blood vessels in a mammal having chronic or acute ischemia. Nor does the present disclosure offer any guidance on any critical core structure or element that these substances need to possess in order to induce the formation of new blood vessels in a mammal having chronic or acute ischemia. Additionally, the instant specification fails to disclose a representative number of species for a broad genus of a vascularization modulating agent. As such, the written description requirement is not satisfied for the instant broadly claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of any vascularization modulating agent other than that of a hematopoietic protein that can mobilize hematopoietic progenitor cells and induce angiogenesis such as GM-CSF, VEGF, SLF, SDF-1, G-CSF, HGF, angiopoietin-1, angiopoetin-2, M-CSF, b-FGF and FLT-3 ligand; and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method

of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

Claims 50-51 and 54-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia, wherein the method comprises administering to the mammal an effective amount of a hematopoietic protein sufficient to form the new blood vessels in the mammal, and increasing endothelial progenitor cell (EPC) frequency to at least about 20% as determined by a standard EPC isolation assay, wherein said hematopoitic protein increases mobilization of hematopoietic progenitor cells and induces angiogenesis,

does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction

or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 50-51 and 55-71 are drawn a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia, wherein the method comprises administering to the mammal an effective amount of a **vascularization modulating agent** sufficient to form new blood vessels in the mammal, and increasing endothelial progenitor cell (EPC) frequency by at least about 20% as determined by a standard EPC isolation assay; the same method wherein the vascularization modulating agent is GM-CSF, M-CSF, b-FGF, SCF, SDF-1, G-CSF, HGF, angiopoietin-1, angiopoietin-2, FLT-3 ligand, or **an effective fragment thereof** or the same method with the various limitations recited in the dependent claims.

The specification teaches by exemplification that intraperitoneal injection of recombinant mouse GM-CSF into mice for 7 days resulted in an increased circulating EPC at day 0 prior to creating a stimulus for neovascularization in treated mice (for this instance the creation of the cornea micropocket and insertion of VEGF pellet). The GM-CSF pretreatment enhanced the neovascularization process observed for treated animals versus untreated animals. Additionally, in a rabbit model of induced hindlimb ischemia, the pretreatment of recombinant human GM-CSF via subcutaneous daily injection for 7 days prior to the development of hindlimb ischemia also resulted in an enhanced EPC mobilization prior to and after the operation, as well as extensive

neovascularization and improved ischemic/normal hindlimb blood pressure ratio following the onset of ischemia, relative to control animals. Utilizing a mouse bone marrow transplantation model, the instant specification also teaches that the EPCs contributing to enhanced corneal neovascularization were specifically mobilized from the bone marrow in response to ischemia and GM-CSF. The specification also discloses the isolation of EPC-enriched cell fractions from mice as Sca-1 antigen positive (Sca-1+) cells, and from rabbits as a cell population depleted of T-lymphocytes, B-lymphocytes and monocytes (TBM^-). These cell populations have been shown to differentiate *in vitro*, and the differentiated cells showed evidence of EC lineage by reaction with BS-1 lectin and uptake of acetylated LDL. Furthermore, upon intravenous administering DiI-labeled Sca-1+ or autologous DiI-labeled TBM^- cells into mouse and rabbit hindlimb ischemia models, respectively, the labeled EPC-derived cells were shown to differentiate *in situ* into ECs as indicated by the co-staining for CD 31 (PECAM) and that the labeled cells were incorporated into colonies, sprouts and capillaries. The specification further teaches that EPC-enriched populations were increased in circulating blood following the onset of induced ischemia in the mouse and rabbit models, and the ischemia-induced EPC mobilization was demonstrated by enhanced ocular neovascularization (monitored by biomicrocopic and fluorescent microscopic examinations) after cornea micropocket surgery in mice with hindlimb ischemia.

The above evidence has been noted and considered. However, the instant specification is not enabled for the instant broadly claimed invention for the following reasons.

The instant claims encompass the utilization of any agent having any chemical structure as encompassed by the term "vascularization modulating agent" to induce the formation of new blood vessels in a mammal having chronic or acute ischemia. The instant specification is not enabled for such a broadly claimed invention for the reasons stated in the lack of Written Description Section above. Briefly, apart from disclosing vascularization modulating agent such as GM-CSF, VEGF, SLF, SDF-1, G-CSF, HGF, angiopoietin-1, angiopoetin-2, M-CSF, b-FGF and FLT-3 ligand, all of which are **hematopoietic proteins that increase mobilization of hematopoietic progenitor cells and induce angiogenesis**, the instant specification fails to disclose any other substances (e.g., carbohydrates, lipids, small organic or inorganic molecules), such that these substances are capable of inducing the formation of new blood vessels in a mammal having chronic or acute ischemia. Therefore, it is a natural flow from the lack of sufficient guidance provided by the present application, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.I

The instant claims encompass the use of any effective fragment of vascularization modulating agents such as GM-CSF, M-CSF, b-FGF, SCF, SDF-1, G-CSF, HGF, angiopoietin-1, angiopoietin-2 and FLT-3 ligand, as well as a fragment of various recited angiogenic proteins in the claimed methods for inducing formation of

new blood vessels in a mammal having chronic or acute ischemia. The specification is not enabled for such a broadly claimed invention. This is because there is a high degree of unpredictability associated with the use of the claimed embodiments, specifically the specification fails to teach which amino acids to be substituted, deleted or inserted, at which positions and in which combinations for the recited vascularization modulating agents, or for the recited angiogenic proteins such that the modified vacularization modulating agents and/or angiogenic proteins still possess the angiogenic activity and/or enhancing the mobilization of endothelial progenitor cells for the induction of new blood vessels formation in the treated mammal. This unpredictability of the broadly claimed invention is further underscored by the absence of information concerning the stability and the proper folding for a functional fragment of a vascularization modulating agent. In discussing peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstaking experimental study (Page 6, first sentence of Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). Furthermore, the relationship between the sequence of a peptide and its tertiary structure associated for its activity is not well understood and is not predictable (Ngo et al., *In* Merz et al., ed. "The protein folding problem and tertiary structure prediction", Birkhauser, 1994). Additionally, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Therefore, in the absence of sufficient guidance provided by the instant specification regarding to the use of any fragment of a vascularization modulating agent or of an angiogenic protein in the methods as claimed, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Accordingly, due to the lack of guidance provided by the specification regarding to the aforementioned issues, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejections in the Amendment filed on January 09, 2002 in Paper No. 8 (pages 6-8) have been fully considered.

With respect to the issue of effective fragments of vascularization modulating agents and angiogenic proteins, Applicants argue basically that one skilled in the art would have been able to use the guidance provided by the instant specification (e.g., various assays including EPC isolation assay, standard hindlimb ischemia assay, standard blood length assay, and standard cornea micropocket assay) to select appropriately effective fragments of the vascularization modulation agents. Applicants

further argue that the cited J.A. Parsons reference is out of date because it is about a quarter of a century old, and it should be withdrawn because many vascularization modulation agents have biological motifs that are readily detected. Applicants' arguments are respectfully found unpersuasive for the following reasons.

Although the Examiner recognizes that various assays are available for monitoring the angiogenic activity and mobilization of endothelial progenitor cells, the main issue still remains that Applicants have not provided sufficient guidance for a skilled artisan on which amino acids to be substituted, deleted or inserted, at which positions and in which combinations for the numerous recited vascularization modulating agents and angiogenic proteins such that the modified vacularization modulating agents and angiogenic proteins still possess the desired angiogenic activity and/or enhancing the mobilization of endothelial progenitor cells for the induction of new blood vessels formation in the treated mammal. The relationship between the sequence of a peptide and its tertiary structure (e.g. its biological activity) is not well understood and is not predictable (Ngo et al., *In* Merz et al., ed. "The protein folding problem and tertiary structure prediction", Birkhauser, 1994), coupled with the recognition that the significance of particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstaking experimental study by Rudinger, together with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention. Additionally, the physiological art is recognized as unpredictable (MPEP

2164.03). The age of the cited Rudinger's reference is irrelevant because Applicants have failed to provide any objective or factual evidence indicating that the making and using of any effective fragment for the numerous vascularization modulating agent and angiogenic proteins for inducing angiogenesis and mobilization of EPCs is routine in the prior art at the effective filing date of the present application.

Accordingly, claims 50-51 and 55-71 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 54, the phrase "by a standard EPC culture 2 5 assay" is unclear. Which assay is that? The metes and bounds of the claim can not be determined.

Claim Rejections - 35 USC § 102

Claims 50, 55-65 and 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Pu et al. (Circulation 88:208-215,1993).

The claims are drawn to a method for inducing formation of new blood vessels in a mammal, wherein the method comprises administration to the mammal an effective amount of a vascularization modulating agent sufficient to form the new blood vessels in

the mammal and increasing endothelial progenitor cells (EPC) frequency by at least about 20% as determined by a standard EPC isolation assay, the same method with various limitations in the dependent claims.

Pu et al. disclose enhanced revascularization of the ischemic limb in a rabbit model of persistent hindlimb ischemia by daily intramuscular injections of endothelial cell growth factor (a-FGF) for 10 days following the postoperative period (see page 209, col. 2, first full paragraph). Enhanced neovascularization quantified by angiograms and a better perfusion in the ischemic limb measured by the calf blood pressure ratio were obtained in the treated animals (See abstract). Since the disclosed method of Pu et al. has the same step as the instant claimed method (administering to a mammal having chronic or acute ischemia an effective amount of a vascularization modulating agent), and because the activity of endothelial cell growth factor in the presence of heparin is just about the same as basic fibrobast growth factor (see page 212, col. 1, first paragraph), one of several vascularization modulating agents or hematopoietic factors contemplated by Applicants, the increase in endothelial progenitor cell frequency and differentiation, as well as an increase in blood vessel length and blood vessel diameter, and an increase in EPC incorporation into foci would be inherent results of the method taught by Pu et al.

Therefore, the reference anticipates the instant claims.

Claims 50-51, 55-67 and 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Franco (U.S. Patent 4,296,100) or Kawakami et al. (Brain Res. 697:104-111, 1995).

Franco teaches a method of treating an area in the heart of a patient subjected to ischemic heart disease to maintain viability in that area for a sustained time period to salvage said area, said method comprising applying an effective dose of FGF (including b-FGF having an isoelectric point of 9.5, and the preferred dosage of about 10 micrograms to 1 gram of FGF per 100 grams of heart which is within the preferred range, 1 ug/kg/day to about 100 ug/kg/day, for *in vivo* dosages of vascularization modulating agents of the presently claimed invention, see col. 1, lines 56-66; col. 2, lines 26-37) to the heart, and wherein the blood flow in said area is increased over that which would occur in the area without treatment with FGF (See examples 1 and 2, and the claims).

Kawakami et al. teach that in an experimental rat model of intracerebral hemorrhage, a local injection of b-FGF (500 to 1000 ng/rat) into the evacuated cavity resulting from early removal of a mass lesion yielded a protective effect against neuronal damage in CA1 pyramidal cells (probably from ischemia due to the transient mass lesion in the caudate nucleus) and an increase of angiogenesis in the evacuated cavity wall (See abstract, and page 108, column 2, fourth paragraph).

Since the disclosed methods of Franco and Kawakami et al. have the same step as the instant claimed method (administering to a mammal having chronic or acute ischemia an effective amount of a vascularization modulating agent), and because b-

FGF is one of several vascularization modulating agents or hematopoietic factors contemplated by Applicants, the increase in endothelial progenitor cell frequency and differentiation, as well as an increase in blood vessel length and blood vessel diameter, and an increase in EPC incorporation into foci would be inherent results of the methods taught by Franco and Kawakami et al.

Therefore, both references anticipate the instant claims.

Claims 50-51, 55-66 and 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferrara et al. (U.S. Patent 6,133,231).

Ferrara et al. disclose methods for enhancing angiogenesis in a mammal suffering from vascular insufficiency or arterial occlusive disease (ischemic conditions) comprising administering to the mammal an effective amount of hepatocyte growth factor (see abstract, and table 1). The effective dosage of the HGF used is in the range from about 1 ug/kg to up to 100 mg/kg of body weight or more per day (col. 5, lines 42-52).

Since the disclosed method of Ferrara et al. has the same step as the instant claimed method (administering to a mammal having chronic or acute ischemia an effective amount of a vascularization modulating agent), and because HGF is one of several vascularization modulating agents or hematopoietic factors contemplated by Applicants coupled with the utilized dosage is within the preferred dosage range of vascularization modulating agents of the presently claimed invention, the increase in endothelial progenitor cell frequency and differentiation, as well as an increase in blood

vessel length and blood vessel diameter, and an increase in EPC incorporation into foci would be inherent results of the method taught by Ferrara et al.

Therefore, Ferrara et al. anticipate the instant claims.

Response to Arguments

Applicants' arguments related to the above rejections in the Amendment filed on January 09, 2002 in Paper No. 8 (page 10) have been fully considered.

Applicants argue that none of the above references discloses a method for inducing formation of new blood vessels **in a mammal having acute or chronic ischemia that involves increasing frequency of EPC by at least about 20% as determined by the standard EPC isolation assay**. Applicants' argument is respectfully found to be unpersuasive because as discussed above the disclosed methods of Pu et al., Franco, Kawakami et al. and Ferrara et al. have the same step as the instant claimed method (administering to a mammal having chronic or acute ischemia an effective amount of a vascularization modulating agent), and because b-FGF, HGF are vascularization modulating agents or hematopoietic factors contemplated by Applicants and since the utilized dosage is within the preferred dosage range of vascularization modulating agents of the presently claimed invention, the increase in endothelial progenitor cell frequency and differentiation, as well as an increase in blood vessel length and blood vessel diameter, and an increase in EPC incorporation into foci would be inherent results of the methods taught by Pu et al., Franco, Kawakami et al. and Ferrara et al.

Accordingly, the claims are rejected for the reasons set forth above.

Claim Rejections - 35 USC § 103

Claims 50-53 and 55-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al. (U.S. Patent 5,880,090, IDS from 09/265041) in view of Asahara et al. (Science 275:964-967, 1997, IDS from 09/265041) or Isner et al. (U.S. Patent No. 5,980,887 with the effective filing date of 11/8/1996).

Hammond et al. teach that upon administering an agent selected from the group consisting of stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) into a graft recipient, bone marrow-derived CD34+ endothelial progenitor cells are mobilized into the blood stream (increase in the concentration of the progenitor cells) and to enhance the endothelialization of synthetic vascular grafts (See abstract and example 3 in column 9). Hammond et al. also teach that more than one endothelialization-promoting agent (e.g., fibroblast growth factors, VEGF, angiopoietin) may be administered concomitantly, and the agent may be administered to the intended graft recipient as much as seven days prior to implantion of the graft, or may begin on the same day as graft implantation (see col. 3, lines 57-67; col. 4, lines 32-40). An exemplified used dosage for G-CSF is from about 5ug to 15 ug/kg body weight for a total of 3 to 5 days (col. 4, lines 24-31), which is within the preferred dosage range of vascularization modulating agents of the presently claimed invention (1 ug/kg/day to about 100 ug/kg/day). Hammond et al. do not teach specifically a method for inducing formation of new blood vessels, or reducing the

severity of blood vessel damage or enhancing EPC mobilization in a mammal having chronic or acute ischemia using GM-CSF. However, Hammond et al. noted that Asahara et al. have shown CD34+ endothelial cell populations are capable of differentiating into endothelial-like cells and the circulating CD34+ or Flk-1+ cells may participate in the repair of ischemic tissue (column 3, lines 28-37). In animal models of ischemia (mouse and rabbit models of induced unilateral hindlimb ischemia), Asahara et al. already teach that syngeneic or autologous endothelial cell progenitors are incorporated into capillaries and small arteries in the neovascular zones of the induced ischemic limb (See abstract and page 966). Isner et al. also teach the use of EC progenitors to induce reendothelialization of an injured blood vessels or treating an injured blood vessel in a patient resulting from surgery (balloon angioplasty or deployment of an endovascular stent) or from an ischemic tissue (e.g. cerebrovascular ischemia, renal ischemia, pulmonary ischemia). Isner et al. further teach the use of EC progenitor cells can be used in combination with an endothelial cell mitogen such as VEGF, FGFs, HGF, nitric oxide synthase among others (see the entire patent and the claims).

Accordingly, at the time of the instant invention it would have been obvious to an ordinary skilled artisan to modify the method disclosed by Hammond et al. by administering into a mammal having an chronic or acute ischemia instead of a recipient of a synthetic vascular graft an agent selected from the group consisting of SCF, GM-CSF and G-CSF to mobilize an effective level of bone marrow-derived endothelial progenitors to home into sites of active angiogenesis to repair ischemic tissues by

forming new blood vessels as taught by Asahara et al. or Isner et al. One of ordinary skilled in the art would have been motivated to carry out the above modification to avoid the tedious and time-consuming isolation and purification of progenitor endothelial cells. Since the modified method has the same step and same active components (e.g., GM-CSF, G-CSF, SCF) with an effective dosage within the preferred dosage range of vascularization modulating agents used in the presently claimed invention, the modified method would also result in an increase in endothelial progenitor cell frequency and differentiation, as well as an increase in blood vessel length and blood vessel diameter, and an increase in EPC incorporation into foci in the treated mammal.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejections in the Amendment filed on January 09, 2002 in Paper No. 8 (pages 11-12) have been fully considered.

Applicants argue that there was substantial doubt as to whether it was possible to promote new blood vessel growth by administering EPCs according to Asahara and Applicants' disclosure. Additionally, Applicants argue the EPCs were thought to have problems responding to cytokines (e.g., GM-CSF taught by Hammond's) to promote neovascularization. Therefore, there is no reasonable expectation that the modified method would work. Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, with respect to the substantial doubt whether it was possible to promote new blood vessel growth by administering EPCs, the issued U.S. patent 5,980,887 (with an effective filing date of 11/8/1996 and Asahara is a co-inventor) demonstrates that the administration of EPCs into a patient would result in inducing the formation of new blood vessels in an ischemic tissue of the treated patient (see the claims). Do Applicants really question about the patentability of the issued U.S. patent 5,980,887, specifically regarding to the enablement issue?

Secondly, with respect to the issue that EPCs were thought to have problems responding to cytokines. Hammond et al. already showed that administering SCF, GM-CSF and G-CSF into a mammal resulting in the mobilization of bone marrow-derived CD34+ cells into the blood stream and/or the multiplication of endothelial progenitors that enhance the adherence to graft surfaces. This is a factual evidence indicating that bone marrow-derived CD34+ or endothelial progenitors (EPCs) do respond to the administered SCF, GM-CSF and G-CSF.

Accordingly, claims 50-53 and 55-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al. in view of Asahara et al. for the reasons set forth above.

Conclusions

No claims are allow d.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER